UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 18, 2004

MEMORANDUM:

SUBJECT: Review the Study, Estimating the Soil Adsorption Coefficient (K_{oc}) for a Series of Biocides by High Performance Liquid Chromatography (HPLC) Using OECD Method 121

TO: Marshall Swindell, Product Manager, Team 33
Regulatory Management Branch I
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THRU: Siroos Mostaghimi, Acting Team Leader, Team One
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DP Barcode: D293377   **EPA Reg. No.:** 464-713
Decision #: 332318   **MRID No.:** 459009-01
Case Type: Adverse Data 6(a)(2)   **Data Submitter:** The Dow Chemical Company
PC Code: 129017   **CAS#:** 643-79-8
Chemical Name: 1,2-Benzenedicarboxaldehyde   **Common Name**: ortho-pthalaldehyde

INTRODUCTION:

Pursuant to Section 6(a)(2) of the Federal Insecticide and Rodenticide Act (FIFRA) as amended, 7 U.S.C. Section 138d(a)(2), the Dow Chemical Company has submitted the Estimated Adsorption Coefficient (log K_{oc}) values for a series of biocides including ortho-phthalaldhyde (1,2-Benzenedicarboxaldehyde) an active ingredient in Ucarcide[TM] P200 Antimicrobial, EPA Reg. No. 464-713. The submitted 6(a)(2) Data has undergone review by Srinivas Gowda of Antimicrobials Division's Risk Assessment and Science Support Branch. The registrant used the OECD Test Guideline 121 to estimate the Adsorption Coefficient (K_{oc}) of various biocides including 1,2-Benzenedicarboxaldehyde (ortho -phthaladehyde) by High Performance Liquid Chromatography (HPLC).

BACKGROUND:

1,2-Benzenedicarboxaldehyde (ortho -phthaladehyde) is an active ingredient in Ucarcide[TM] P200 Antimicrobial, EPA Reg. No. 464-713. The product is recommended for use by manufacturers in formulating industrial bactericides and preservatives. The submitted study was conducted to estimate the Adsorption Coefficient (log K_{oc}) of various biocides, including the active ingredient, ortho-phthaladehyde using High Performance Liquid Chromatography (HPLC).

The study entitled "Estimating the Soil Adsorption Coefficient (K_{oc}) for a Series of Biocides by High Performance Liquid Chromatography (HPLC) Using OECD Method 121" by S.J. Gonsior, M.A. Rivard, and M.K. Stock, Environmental Chemistry Research Laboratory, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland Michigan 48674, Study No. 011094, dated November 22, 2002, has been submitted to the Agency (MRID Number 459009-01) persuant to Section 6(a)(2) of the Federal Insecticide and Rodenticide Act (FIFRA) as amended, 7 U.S.C. Section 138d(a)(2).

METHODOLOGY:

The purpose of this study was to estimate the adsorption coefficient (K_{oc}) of series of biocides including ortho-phthalaldhyde (1,2-Benzenedicarboxaldehyde) an active ingredient in Ucarcide[TM] P200 Antimicrobial, EPA Reg. No. 464-713 using the HPLC estimation method. The study was conducted according to the procedures specified in the Organization for Economic Cooperation and Development (OCDE/OECD) Guideline for Testing of Chemicals, Guideline 121.

I.   MATERIALS AND METHODS

GUIDELINE FOLLOWED: The soil adsorption coefficients (K_{oc}) for a series of biocides were estimated using OECD Method 121 "Estimation of the Adsorption Coefficient (K_{oc}) on Soil and Sewage Sludge Using High Performance Liquid Chromatography (HPLC)."

COMPLIANCE: All phases of this study were conducted in compliance with GLP

standards (Title 40 CFR, Part 160 and Part 792), OECD Standard ENV/MC/CHEM(98)17, and EC Directive 99/11/EC (OJ No. L 77/9-21, 23/3/1999) with the following exceptions: 1) GLP characterization of the identity and purity of the test material was performed concurrent with the study; 2) characterization of the identity and purity for 2 of the 13 test materials was performed by laboratories that do not operate under GLP guidelines; and 3) characterization of the identity and purity of the reference compounds was performed by a laboratory that does not operate under GLPs. Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

A. **MATERIALS**:

1. **Test Material**   A series of biocides were analyzed in this study and are listed in the table below.

Product Name	Chemical Name	CAS Number
TRIS NITRO	tris(hydroxymethyl)nitromethane	126-11-4
BIOBAN CS-1135	4,4-dimethyl-oxazolidine	51200-87-4
BIOBAN CS-1246	7-ethyl bicyclooxazolidine	7747-35-5
BRONOPOL	2-bromo-2-nitro-1,3-propanediol	52-51-7
BIOBAN DXN	2,6-dimethyl-m-dioxan-4-ol Acetate	828-00-2
DBNPA 100 PTECH	2,2-dibromo-3-nitrilopropionamide	3039547
OPA	o-phthalaldehyde	643-79-8
BIOBAN P1487	4-(2-nitrobutyl)-morpholine	2224-44-4
	(2-ethyl-2-nitromethylene)-dimorpholine	1854-23-5
AMICAL 48	Diodomethyl-p-tolysulfone	6617702

DOWICIL 150	cis-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride	51229-78-8
DOWICIL 75	cis/trans-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride	4080-31-3
DOWICIDE 1	orthophenylphenol	90-43-7
BIOBAN BNS	bromonitrostyrene	7166-19-0

Description: MilliQ water was used in preparation of the test materials and reference compound stock solutions. Twelve of the thirteen biocides used in the study were provided by The Dow Chemical Company; ortho-phthalaldehyde was obtained from Sigma-Aldrich Fine Chemicals (Milwaukee, Wisconsin).

Purity:

Chemical Name	Lot./Batch No.	Analytical Purity
tris(hydroxymethyl)nitromethane	ANGUS 050101	101.4%
4,4-dimethyl-oxazolidine	1H25-DF87	66.0%
7-ethyl bicyclooxazolidine	PA0531LAN3	96.9%
2-bromo-2-nitro-1,3-propanediol	SKF-PO015-00-001N	98.6%
2,6-dimethyl-m-dioxan-4-ol Acetate	OD0131LA30	94.3%
2,2-dibromo-3-nitrilopropionamide	OF0801QT01	99.5%
o-phthalaldehyde	100K1480	98.0%
4-(2-nitrobutyl)-morpholine (2-ethyl-2-nitromethylene)-dimorpholine	OJ0431LAN7	86.3%

Diodomethyl-p-tolysulfone	NB0231LA02	98.8%
cis-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride	NH1901QT1P	99.3%
cis/trans-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride	OK1701QT1P	32.7% cis- 34.9% trans-
orthophenylphenol	K0039	99.9%
bromonitrostyrene	RM-426-70-A	99.7%

2. Soil Characteristics

Soils were not used in this study. The adsorption constant was determined by the HPLC estimation method (OECD 121).

B. STUDY DESIGN:

1. Definitive study experimental and analytical conditions:

The HPLC estimation method uses an analytical column containing a stationary phase composed of cyanopropyl groups bonded onto silica. This stationary phase contains both polar and non-polar sites. The interactions between the test compound and the polar and non-polar sites in the stationary phase are theorized to be similar to the interactions of the test compound with the organic matter in soil. Thus, it is assumed that a correlation between a compound's retention time on the HPLC column and its adsorption coefficient on organic matter in soil can be established using a series of reference compounds with experimentally determined K_{oc} values. The log K_{oc} values for a series of biocides were estimated using the HPLC estimation method. The results were compared to estimates obtained from two commercially available computer programs that estimate K_{oc} values using quantitative structure activity relationships (QSARs).

Sample analysis was conducted using an HPLC system (Agilent 1100 Series, Agilent Technologies, Palo Alto, California) with variable wavelength detection under the following conditions:

Column:	ZORBAX SB-CN; 4.6 x 250 mm; 5-micron packing
Detector:	G1314A Variable wavelength detector - 210 nm
Mobile Phase:	Methanol:water (55:45; v:v); non-buffered
	Methanol:0.01M aqueous buffer (phosphate, pH 6.0) (55:45; v:v); buffered
Flow Rate:	1.0 mL/minute
Pump:	G1312A Binary Pump
Injector:	G1313A Autosampler

The average time for a solvent molecule to pass through the HPLC column (t_0) was determined by duplicate analyses of solutions containing urea or sodium nitrate, as these compounds are not retained on the column under the test conditions. A calibration standard was prepared with seven compounds and analyzed at regular intervals. The retention time for each of the reference compounds was determined. To ensure the reproducibility of compound retention times in the HPLC assay, the HPLC column was covered with foam insulation to minimize temperature changes during analysis.

Stock solutions of the test compounds were prepared in methanol, and diluted in the mobile phase for analysis. Concentrations of the compounds in the test solutions were adjusted to an approximate nominal concentration of 10 mg/L. For BIOBAN CS-1135 and BIOBAN CS-1246, the concentration was increased to 100 mg/L to obtain adequate sensitivity in the assay. The test solutions were analyzed in duplicate and retention times for each test compound were determined.

2. <u>Description of analytical procedures:</u>

The analytical procedures and methodology were one in the same for this study as the experimental procedure included running the samples on a HPLC system.

The pH of the aqueous solutions was determined with an Orion 501A pH meter equipped with a combination pH electrode which was calibrated with standard buffer solutions. The temperature measurements were monitored using a laboratory temperature monitoring system.

II.   <u>RESULTS AND DISCUSSION</u>

A. <u>**TEST CONDITIONS**</u>:

The test conditions appear to have been maintained throughout the study. The HPLC column was covered with foam insulation to minimize temperature changes. The column temperature was recorded during the analysis. The temperatures recorded during the HPLC analyses ranged from 23.2 to 25.2°C.

Table 1: Estimated Log K_{oc} Values for Thirteen Biocides Determined by HPLC and Quantitative Structure Activity Models

Product Name	Retention Time (minutes)[a]	Regression Equation	Estimated pKa (ACD Labs)	Estimated Log K_{oc} by HPLC	Estimated Log K_{oc} by QSAR (Syracuse Research Corporation)	Estimated Log K_{oc} by QSAR (ACD Labs)
TRIS NITRO	2.92	Log K_{oc} = 2.8373 (Log k') + 1.0198	12.3 ± 0.1	0.6	1	1.4
BIOBAN CS-1135	3.47	Log K_{oc} = 2.7966 (Log k') + 1.5105	8.4 ± 0.4	1	0.8	1.3
BIOBAN CS-1246	3.5	Log K_{oc} = 2.7749 (Log k') + 1.5433	5.2 ± 0.4	1	1	1.5
BRONOPOL	3.34	Log K_{oc} = 2.8206 (Log k') + 1.0964	12.0 ± 0.1	1	0	2.3
BIOBAN DXN	3.7	Log K_{oc} = 2.8189 (Log k') + 1.0946	Not ionizable	1.2	1	1.6
DBNPA 100 PTECH	3.67	Log K_{oc} = 2.9486 (Log k') + 1.0592	11.7 ± 0.5	1.2	1	2.2
OPA	3.62	Log K_{oc} = 2.9486 (Log k') + 1.0592	Not ionizable	1.2	1	1.7
BIOBAN P1487	4.61	Log K_{oc} = 2.5823 (Log k') + 1.5528	6.7 ± 0.1, 5.7 ± 0.1, 6.2 ± 0.1	1.7	1.7	1.8

AMICAL 48	6.62	Log K_{oc} = 2.826 (Log k') + 1.015	Not ionizable	2.3	2.8	3.5
DOWICIL 150	7.05	Log K_{oc} = 2.5837 (Log k') + 1.5541	0.8 ± 0.4	2.5	2.6	—[b]
DOWICIL 75	7.18	Log K_{oc} = 2.5837 (Log k') + 1.5541	0.8 ± 0.4	2.5	2.6	—[b]
DOWICIDE 1	7.68	Log K_{oc} = 2.826 (Log k') + 1.015	10.0 ± 0.1	2.6	4	3
BIOBAN BNS	9.88	Log K_{oc} = 2.8206 (Log k') + 1.0964	Not ionizable	3	3	2.7

[a] Mean of two replicates.

[b] ACD Labs program could not estimate Log K_{oc} based on structure.

B. ADSORPTION:

The HPLC estimated log K_{oc} values were 0.6 (TRIS NITRO), 1.0 (BIOBAN CA-1135), 1.0 (BIOBAN CS-1246), 1.0 (BRONOPOL), 1.2 (BIOBAN DXN), 1.2 (DBNPA 100 PTECH), 1.2 (OPA), 1.7 (BIOBAN P1487), 2.3 (AMICAL 48), 2.5 (DOWICIL 150), 2.5 (DOWICIL 75), 2.6 (DOWICIDE 1), and 3.0 (BIOBAN BNS). The log K_{oc} from the HPLC estimation was in very close agreement with the QSAR models, particularly, the Syracuse Research Corporation Model. The average difference in estimated log K_{oc} values between the HPLC estimate and the QSAR estimate was 0.3 ± 0.4 log units for the SRC program and 0.6 ± 0.4 log units for the ACD Labs program.

III.   SUMMARY OF DATA:

The K_{oc} values for thirteen biocides were estimated using an HPLC estimation method and quantitative structure activity relationships (QSAR). The experiment was conducted in accordance with OECD Method 121 "Estimation of the Adsorption Coefficient (K_{oc}) on Soil and Sewage Sludge Using High Performance Liquid Chromatography (HPLC)", and in compliance with the GLP standards (Title 40 CFR, Part 160 and Part 792), OECD Standard ENV/MC/CHEM(98)17 and EC Directive 99/11/EC (OJ No. L 77/9-21, 23/3/1999). The log K_{oc} values for the series of biocides were determined using an HPLC estimation method by comparing the chromatographic retention times of the test compound with a series of reference compounds. The HPLC system used was the Agilent 1100 Series with a ZORBAX SB-CN column and variable wavelength detection. The results were compared to estimates obtained from two commercially available computer programs that estimated K_{oc} values using quantitative structure activity relationships (QSARs).

The HPLC estimated log K_{oc} values were 0.6 (TRIS NITRO), 1.0 (BIOBAN CA-1135), 1.0 (BIOBAN CS-1246), 1.0 (BRONOPOL), 1.2 (BIOBAN DXN), 1.2 (DBNPA 100 PTECH), 1.2 (OPA), 1.7 (BIOBAN P1487), 2.3 (AMICAL 48), 2.5 (DOWICIL 150), 2.5 (DOWICIL 75), 2.6 (DOWICIDE 1), and 3.0 (BIOBAN BNS). The log K_{oc} from the HPLC estimation was in very close agreement with the QSAR models, particularly, the Syracuse Research Corporation Model. The average difference in estimated log K_{oc} values between the HPLC estimate and the QSAR estimate was 0.3 ± 0.4 log units for the SRC program and 0.6 ± 0.4 log units for the ACD Labs QSAR model.

Results Synopsis:

Product/Chemical: TRIS NITRO; tris(hydroxymethyl)nitromethane

Estimated log K_{oc} (HPLC): 0.6

Estimated log K_{oc} (SRC): 1

Estimated log K_{oc} (ACD Labs): 1.4

Product/Chemical: BIOBAN CS-1135; 4,4-dimethyl-oxazolidine

Estimated log K_{oc} (HPLC): 1

Estimated log K_{oc} (SRC): 0.8

Estimated log K_{oc} (ACD Labs): 1.3

Product/Chemical: BIOBAN CS-1246; 7-ethyl bicyclooxazolidine

Estimated log K_{oc} (HPLC): 1

Estimated log K_{oc} (SRC): 1

Estimated log K_{oc} (ACD Labs): 1.5

Product/Chemical: BRONOPOL; 2-bromo-2-nitro-1,3-propanediol

Estimated log K_{oc} (HPLC): 1

Estimated log K_{oc} (SRC): 0

Estimated log K_{oc} (ACD Labs): 2.3

Product/Chemical: BIOBAN DXN; 2,6-dimethyl-m-dioxan-4-ol Acetate

Estimated log K_{oc} (HPLC): 1.2

Estimated log K_{oc} (SRC): 1

Estimated log K_{oc} (ACD Labs): 1.6

Product/Chemical: DBNPA 100 PTECH; 2,2-dibromo-3-nitrilopropionamide

Estimated log K_{oc} (HPLC): 1.2

Estimated log K_{oc} (SRC): 1

Estimated log K_{oc} (ACD Labs): 2.2

Product/Chemical: OPA; o-phthalaldehyde

Estimated log K_{oc} (HPLC): 1.2

Estimated log K_{oc} (SRC): 1

Estimated log K_{oc} (ACD Labs): 1.7

Product/Chemical: BIOBAN P1487; 4-(2-nitrobutyl)-morpholine; (2-ethyl-2-nitromethylene)-dimorpholine

Estimated log K_{oc} (HPLC): 1.7

Estimated log K_{oc} (SRC): 1.7

Estimated log K_{oc} (ACD Labs): 1.8

Product/Chemical: AMICAL 48; Diodomethyl-p-tolysulfone

Estimated log K_{oc} (HPLC): 2.3

Estimated log K_{oc} (SRC): 2.8

Estimated log K_{oc} (ACD Labs): 3.5

Product/Chemical: DOWICIL 150; cis-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride

Estimated log K_{oc} (HPLC): 2.5

Estimated log K_{oc} (SRC): 2.6

Estimated log K_{oc} (ACD Labs): NA

Product/Chemical: DOWICIL 75; cis/trans-1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride

Estimated log K_{oc} (HPLC): 2.5

Estimated log K_{oc} (SRC): 2.6

Estimated log K_{oc} (ACD Labs): NA

Product/Chemical: DOWICIDE 1; orthophenylphenol

Estimated log K_{oc} (HPLC): 2.6

Estimated log K_{oc} (SRC): 4

Estimated log K_{oc} (ACD Labs): 3

Product/Chemical: BIOBAN BNS; bromonitrostyrene

Estimated log K_{oc} (HPLC): 3

Estimated log K_{oc} (SRC): 3

Estimated log K_{oc} (ACD Labs): 2.7

Study Acceptability: This study was conducted according to the OECD Guideline 121 Estimation of Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC). This procedure is not a recommended procedure of Office of Pesticide Programs. Therefore, this study is considered a screening study and is unacceptable for use in supporting registration of this chemical.

RASSB's CONCLUSIONS AND RECOMMENDATIONS:

The submitted HPLC Test reflects the guidelines specified by the OECD 121, High Performance Liquid Chromatography (HPLC) Method for the Estimation of Adsorption Coefficient (K_{oc}) in Soil. The estimated log K_{oc} values for the biocides are as follows:

Biocides	**log K_{oc} (HPLC)**	
TRIS NITRO; tris(hydroxymethyl)nitromethane	0.6	
BIOBAN CS-1135; 4,4-dimethyl-oxazolidine		1.0
BIOBAN CS-1246; 7-ethyl bicyclooxazolidine	1.0	
BRONOPOL; 2-bromo-2-nitro-1,3-propanediol	1.0	
BIOBAN DXN; 2,6-dimethyl-m-dioxan-4-ol Acetate		1.2
DBNPA 100 PTECH; 2,2-dibromo-3-nitrilopropionamide		1.2
OPA; o-phthalaldehyde	1.2	
BIOBAN P1487; 4-(2-nitrobutyl)-morpholine		
(2-ethyl-2-nitromethylene)-dimorpholine		1.7
AMICAL 48; Diodomethyl-p-tolysulfone		2.3

DOWICIL 150; cis-1-(3-chloroallyl)-3,5,7-triaza-1-

        azoniaadamantane chloride   2.5

DOWICIL 75; cis/trans-1-(3-chloroallyl)-3,5,7-triaza-1-

        azoniaadamantane chloride   2.5

DOWICIDE 1; orthophenylpheno   2.6

BIOBAN BNS; bromonitrostyrene   3.0

The estimated log K_{oc} (HPLC) values for these biocides were in good agreement with estimates from two different computer programs that predict log K_{oc} values using the Quantitative Structure Activity Models.

Risk Assessment and Science Support Branch (RASSB) concludes that the estimation method described in the OECD Test Guideline 121 cannot fully replace the US Environmental Protection Agency's actual Adsorption/Desorption study in soil (Pesticide Assessment Guidelines, Subdivision N, §163-1) for the determination of the K_{oc} values of the pesticides. This study is considered unacceptable to support registration of this chemical. It is essentially a screening study for batch equilibrium studies.

cc: Srinivas Gowda/RASSB/AD

    Chemical File (129017)/AD

Sign-off Date   : 03/18/04
DP Barcode No.: D293377